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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,897	07/31/2001	Masashi Ogawa	Q65704	2025

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EXAMINER	
MORAN, MARJORIE A	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,897	OGAWA ET AL.	
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over SALTHOUSE et al. (Experientia (1970) vol. 26 (2), pp. 220-221) in view of GALIS et al. (FASEB (7/1995), volume 9, pages 974-980) and BATTISTA (US 3,649,347).

Claim 3 recites a method of detecting a protease in a biological sample by contacting one of multiple continuous slices of the sample with a thin membrane comprising a protease substrate and a hardener on a support, contacting the

remaining slices of the sample with a similar thin membrane which also comprises a protease inhibitor, detecting traces of digestion on the membranes, and comparing the two. Claim 21 limits the cross-linkers to a recited list.

SALTHOUSE teaches a method for detecting protease in a sample wherein tissue sections are contacted with a dried thin membrane comprising collagen dried on a support, and comparing digestion of the collagen to digestion of collagen soaked in a protease inhibitor (p. 221). SALTHOUS E does not specifically teach cross-linking agents nor sections which are "substantially continuous".

GALIS teaches a method of detecting a protease in a biological sample wherein consecutive sections of the sample are brought into contact with a thin membrane comprising a support holding a fluorescent substrate mixed with a protease substrate, and other sections are brought into contact with similar thin membranes with protease inhibitors incorporated, and the results from the two are compared (p. 975: Protocol and Controls).

BATTISTA teaches a variety of cross-linkers for collagen and teaches that cross-linking may improve the properties of thin films comprising the collagen (col. 6, lines 29-50). BATTISTA specifically teaches many of the cross-linkers recited in claim 21 (col. 6, lines 29-36). BATTISTA specifically teaches that his cross-linked collagen may successfully be applied to a variety of supports, including glass and films (col. 5, lines 10-29).

It would have been obvious to one of ordinary skill in the art at the time of invention to have contacted the slides of SALTHOUSE in the method of

SALTHOUSE with consecutive sections of sample, as taught by GALIS, where the motivation would have been to assay for enzyme activity across a series of tissue slices, as taught by the method of GALIS and suggested by the cryostat slices and tissue sections of SALTHOUSE. It would further have been obvious to have added the cross-linking agents of BATTISTA to the collagen on the supports/slides in the method of SALTHOUSE where the motivation would have been to improve the properties of the collagen, as taught by BATTISTA. One skilled in the art would reasonably have expected success in incorporating the cross-linkers of BATTISTA with the collagen in the method of SALTHOUSE because BATTISTA teaches that his cross-linked collagen may successfully be used on a variety of surfaces and for a variety of purposes, as set forth above.

Claims 5 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over SALTHOUSE et al. (Experientia (1970) vol. 26 (2), pp. 220-221) in view of BATTISTA (US 3,649,347) and LAWRENCE et al. (IDS ref: US 5,416,003).

Claim 5 recites a method wherein a sample (not limited to be slices) is contacted by a thin membrane comprising layers laminated together on a support, wherein one layer comprises a protease substrate and a hardener, and a second layer comprises a substrate, hardener, and inhibitor, and the traces of digestion on the two layers are detected and compared. Claim 22 limits the cross-linkers to a recited list.

SALTHOUSE teaches a method for detecting protease in a sample wherein tissue sections are contacted with a dried thin membrane comprising collagen dried on a support, and comparing digestion of the collagen to digestion of collagen soaked in a protease inhibitor (p. 221). SALTHOUS E does not specifically teach cross-linking agents nor a multiply layered film.

BATTISTA teaches a variety of cross-linkers for collagen and teaches that cross-linking may improve the properties of thin films comprising the collagen (col. 6, lines 29-50). BATTISTA specifically teaches many of the cross-linkers recited in claim 22 (col. 6, lines 29-36). BATTISTA also specifically teaches that his cross-linked collagen may successfully be applied to a variety of supports, including glass and films (col. 5, lines 10-29), and teaches that his collagen may be used on multiply layered substrates (col. 5, lines 30-40).

LAWRENCE teaches a device for detecting proteases in samples wherein multiple layers are laminated together, and wherein one layer may comprise a substrate and another layer may comprise an inhibitor (col. 23, lines 55-62 and col. 24, lines 34-39).

It would have been obvious to one of ordinary skill in the art at the time of invention to have laminated a layer comprising a substrate, hardener, and inhibitor to a layer comprising a substrate, hardener, and inhibitor in a multiplayer analytical element, as taught by LAWRENCE, for use in the method of SALTHOUSE where the motivation would have been to facilitate measurement of protease in a single sample using a single test element, as suggested by the teaching of LAWRENCE that a test element comprising laminated layers can be

used to detect proteases. It would further have been obvious to have used included any of the crosslinkers BATTISTA in a multiply layered test element in the method made obvious by SALTHOUSE and LAWRENCE where the motivation would have been to improve the properties of the collagen, as taught by BATTISTA. One skilled in the art would reasonably have expected success in incorporating the cross-linkers of BATTISTA with collagen in a multiply-layered element for use in a method to detect proteases because BATTISTA teaches that his cross-linked collagen may successfully be used in multiply-layered elements, LAWRENCE teaches that multiply-layered elements may be used to detect proteases, and SALTHOUSE teaches that collagen can be used to detect proteases.

Applicant's arguments filed 5/24/04 have been fully considered but they are not persuasive. Applicant's argument that SALTHOUSE does not teach a cross-lining agent is an accurate one; however, as admitted by applicant, BATTISTA does teach cross-linkers to be added to collagen on thin films. In response to the argument that one skilled in the art would not have been motivated to add the cross-linkers of BATTISTA to improve the "wet-strength" of the dried device of SALTHOUSE, it is noted that BATTISTA also teaches dried devices comprising collagen and cross-linkers, and teaches that the increase in wet-strength is an improvement seen upon addition of "wet" samples (col. 6). As protease may be detected in tissues and bodily fluids, both of which are generally considered "wet" samples by those skilled in the art, and SALTHOUSE

specifically teaches detection is tissue slices, the examiner maintains that one skilled in the art would have been motivated to increase the "wet-strength" of the collagen of SALTHOUSE by adding one of the cross-linkers of BATTISTA. Further, it is noted that BATTISTA teaches other motivations for adding cross-linkers, as admitted by application on pages 7-8 of the response. In response to the argument that improved heat resistance is "not relevant" to the instant claims, it is noted that the instant claims fail to recite any limitation with regard to temperature, therefore the argument set forth by applicant is moot.

In summary, and in response to applicant's argument that increased wet-strength and heat resistance are "not relevant", the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to the argument that the cross-linking agents of applicant provide an unexpected advantage, or improvement, over the prior art, it is noted that there is no evidence for an increased degree of "control" of sensitivity over the membranes suggested *by the prior art*. Applicant points to Table 5 for evidence that protease digestion is reduced in the presence of increasing amounts of cross-linker. Table 5 indicates that sample 116 and 117 have a membrane thickness of 0.0 μm while sample 118 has a membrane thickness of 0.8 μm - a substantial increase in thickness. It is well known in the art that a change in "thickness" of a sample changes its optical density. Further, it is noted

that while samples 116 and 117 have differing concentrations of cross-linker (117 has 3 times more than 116), there is no commensurate change in optical density between these samples. Thus, the change is optical density between sample 118 versus samples 116 and 117 appears to be due to a change in membrane thickness, not to the difference in cross-linker concentration. Thus, applicant's argument that one may control the DEGREE of digestion by changing cross-linker concentration is not supported by the evidence and is not persuasive. Further, it is unclear from either applicant's arguments or the putative evidence that a DECREASE in protease digestion would be an improvement. Based on the disclosure of the specification (pp. 1-4), it appears that an INCREASE in digestion (i.e. a "faster" assay) is desired.

In addition, it is noted that the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). See MPEP 716.02 (d). Although there is no evidence comparing the instant devices to those of the prior, it is noted that the "evidence" indicated by applicant is for films comprising acid extracted swine gelatin or collagen IV in specific ratios to 1,2-Bis(vinylsulfonyl-acetamido)ethane on PET supports. The claims are not limited to comprise these combinations of protease, cross-linker and support.

For these reasons, the rejections of claims 3 and 5 is maintained, and claims 21-22 are rejected.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over SALTHOUSE et al. (Experientia (1970) vol. 26 (2), pp. 220-221) in view of GALIS et al. (FASEB (7/1995), volume 9, pages 974-980) and BATTISTA (US 3,649,347) as applied to claims 3 and 21 above, and further in view of SPECHT et al. (US 5,219,992).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over SALTHOUSE et al. (Experientia (1970) vol. 26 (2), pp. 220-221) in view of BATTISTA (US 3,649,347) and LAWRENCE et al. (IDS ref: US 5,416,003) as applied to claims 5 and 22 above, and further in view of SPECHT et al. (US 5,219,992).

The claims recite methods of detecting a protease in a sample, as set forth above. Claims 19 and 20 limit the cross-linker to one comprising a vinylsulfonyl group.

The combination of SALTHOUSE, GALIS and BATTISTA and the combination of SALTHOUSE, BATTISTA and LAWRENCE make obvious methods of detecting a protease in a sample, as previously set forth an maintained above. BATTISTA teaches a variety of cross-linkers, and further teaches that the choice of cross-linker depends on the end use of the product (col. 6, lines 29-39). None of SALTHOUSE, BATTISTA, GALIS or LAWRENCE teach a cross-linking agent which comprises a vinylsulfonyl group.

SPECHT teaches thin films for use as chemical analyzers which comprise vinylsulfonyl cross-linkers, and specifically teaches that these hardeners are preferred in multi-layer elements (abstract and col. 9, lines 3-33). SPECHT

teaches that his cross-linkers may be used with either gelatin or collagen (col. 1, lines 19-21).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used a vinylsulfonyl-comprising cross-linker, as taught by SPECHT, as the cross-linker in the method of SALTHOUSE, GALIS and BATTISTA or in the method of SALTHOUSE, BATTISTA and LAWRENCE where the motivation would have been to use any hardener known in the art for cross-linking gelatin or collagen, as taught by both BATTISTA and SPECHT (col. 1, lines 54-60). No criticality or unexpected result has been shown for the use of a vinylsulfonyl hardener over other cross-linkers known in the art; e.g. those specifically taught by BATTISTA.

Conclusion

Claims 3, 5 and 19-22 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

8/13/04